NDA 20-083/S-025

Janssen Research Foundation
Attention: Edward G. Brann
Asst. Director, Regulatory Affairs
1125 Trenton-Harbourton Rd.
P. O. Box 200
Titusville, NJ 08560-0200

Dear Mr. Brann:

Please refer to your supplemental new drug application dated November 29, 1999, received November 30, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sporanox® (itraconazole) Capsules, 400 mg.

We acknowledge receipt of your submissions dated January 19, 2001, March 26, 2001, April 16, 2001 and May 2, 2001.

This supplemental new drug application provides for changes to the Sporanox® Capsule label as summarized below:

1. Information concerning congestive heart failure in patients receiving Sporanox® has been added to the **Boxed Warning, CLINICAL PHARMACOLOGY/Special Populations/Decreased Cardiac Contractility, CONTRAINDICATIONS/Congestive Heart Failure, WARNINGS/Cardiac Dysrythmias, WARNINGS/Cardiac Disease, PRECAUTIONS/Information for Patients** and **ADVERSE REACTIONS/Post-marketing Experience.**

2. Dofetilide has been added to the list of **Drug Interactions** in the **Black Box, CONTRAINDICATIONS/Drug Interactions,** and **PRECAUTIONS/ Drug Interactions/Antiarrythmics**. Astemizole has been deleted from these sections of the label and the **PRECAUTIONS/Drug Interactions/Antihistamine** statement regarding astemizole has also been deleted.

3. Information describing Sporanox® as a CYP3A4 inhibitor causing increased plasma concentration levels of certain co-administered drugs has been added to the **Boxed Warnings, CONTRAINDICATIONS/Drug Interactions** and **PRECAUTIONS/ Drug Interactions.** This information has also been added to the following drug classes in **PRECAUTIONS/ Drug Interactions: Anticonvulsants, Antimycobacterials, Antipsychotics, Macrolide Antibiotics, Non-nucleoside Reverse Transcriptase Inhibitors, Protease Inhibitors** and alfentanil and trimetrexate listed in the **"Other"** category.

4. A statement has been added to **INDICATIONS AND USAGE** advising that prior to initiating treatment, appropriate nail specimens for laboratory testing (KOH preparation, fungal culture, or nail biopsy) should be obtained to confirm the diagnosis of onychomycosis.

5. Information concerning hepatotoxicity in patients receiving Sporanox® has been added to **CLINICAL PHARMACOLOGY/Special Populations/Hepatic Insufficiency, CONTRAINDICATIONS/Hepatitis, WARNINGS/Hepatic Effects, ADVERSE REACTIONS** and **ADVERSE REACTIONS/Post-marketing Experience.**

6. The **CLINICAL PHARMACOLOGY/Special Populations/Renal Insufficiency** subsection was revised to provide a more complete description of the results of the pharmacokinetic study in renally impaired patients.

7. Information concerning the negative inotropic effect of dihydropyridine calcium channel blockers in patients receiving Sporanox® has been added to **PRECAUTIONS/Calcium Channel Blockers**.

8. The following drugs have been added to **PRECAUTIONS/Drug Interactions:**

    - alfentanil
    - alprazolam
    - atorvastatin
    - busulfan
    - buspirone
    - cerivastatin
    - clarithromycin
    - docetaxel
    - dofetilide
    - erythromycin
    - nevirapine
    - omeprazole
    - pimozide
    - saquinavir
    - sirolimus
    - trimetrexate
    - verapamil

    Additionally, this section has been reorganized to include new class names.

9. Menstrual disorders was added to rare cases described in **ADVERSE REACTIONS/Post-marketing Experience.**

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (package insert submitted May 2, 2001). We acknowledge that the initial printing will not include menstrual disorders in the **PRECAUTIONS** section, **Post-marketing Experience** subsection, but menstrual disorders will be included in the subsequent printing.

Please submit the final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-083/S-025." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of any promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

If an additional letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Robin Anderson, Labeling Reviewer, at (301) 827-2127.

Sincerely,

Mark J. Goldberger, M.D., M.P.H.
Director
Division of Special Pathogen and Immunologic Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research